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Alternatives to Phosphinooxazoline (^{t}BuPHOX) Ligands in the Metal-Catalyzed Hydrogenation of Minimally Functionalized Olefins and Cyclic β-Enamides

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Abstract. This study presents a new series of readily accessible iridium- and rhodium-phosphite/oxazoline catalytic systems that can efficiently hydrogenate, for the first time, both minimally functionalized olefins and functionalized olefins (62 examples in total) in high enantioselectivities (ee's up to >99%) and conversions. The phosphite-oxazoline ligands, which are readily available in only two synthetic steps, derive from previous privileged 4-alkyl-2-[2-(diphenylphosphino)phenyl]-2-oxazoline (PHOX) ligands by replacing the phosphine moiety by a biaryl phosphite group and/or the introduction of a methylene spacer between the oxazoline and the phenyl ring. The modular design of the ligands have given us the opportunity not only to overcome the limitations of the iridium-PHOX catalytic systems in the hydrogenation of minimally functionalized *Z*-olefins and 1,1-disusbtituted olefins, but also to expand their use to unfunctionalized olefins containing other challenging scaffolds (e.g., exocyclic benzofused and triaryl substituted olefins) and also to olefins with poorly coordinative groups (e.g., α,β unsaturated lactams, lactones, alkenylboronic esters, ...) with enantioselectivities typically >95% ee. Moreover, both enantiomers of the hydrogenation product could be obtained by simply changing the configuration of the biaryl phosphite moiety. Remarkably, the new catalytic systems also provided excellent enantioselectivities (up to 99% ee) in the asymmetric hydrogenation of another challenging class of olefins – the functionalized cyclic β-enamides. Again, both enantiomers of the reduced amides could be obtained by changing the metal from Ir to Rh. We also demonstrated that environmentally friendly propylene carbonate can be used with no loss of enantioselectivity. Another advantage of the new ligands over the PHOX ligands is that the best ligands are derived from the affordable (*S*)-phenylglycinol rather than from the expensive (*S*)-*tert*-leucinol.

Keywords: Hydrogenation; unfunctionalized olefins; cyclic β-enamides; rhodium; iridium

Introduction

The demand for enantiomerically pure chemicals (i.e. drugs, agrochemicals, flavors ...) has stimulated the search for efficient synthetic methodologies.[1] Among them, transition-metal based asymmetric catalysis is a reliable, selective, and atom-economic strategy to access optically pure compounds.[1] The catalyst's ability to transfer the chiral information to the product depends on key reaction parameters that must be optimized in order to achieve the desired activity and selectivity.[1] The ligand structure plays a central role in the catalyst's performance, in which an electronically and sterically well defined scaffold is the most important factor.[1,2] In this context, thousands of chiral ligands have been developed although only few of them - called privileged ligands - have a general scope.[2,3] Broad substrate and reaction scopes are desirable to reduce time consuming ligand design and synthesis. Phosphine-oxazoline PHOX ligands are considered privileged ligands. They have been successfully applied in asymmetric metal-catalyzed reactions such as hydrogenation, Heck coupling and allylic substitution reactions among others.[4] PHOX ligands have also the advantage that they are prepared from amino alcohols in just two steps. However, the catalyst that has provided the best enantiomeric excesses in most processes is the *tert*-leucinol-derived PHOX (^{t}BuPHOX) ligand. One drawback of ^{t}BuPHOX (and of other state-of-the-art oxazoline-based ligands) is that the high cost of the *tert*-leucinol as starting material makes them less appealing for industrial scale application. Another limitation is that the free PHOX ligands are prone to oxidation. Although related phosphine-oxazoline ligands have been developed to solve these limitations (such as SimplePHOX, ThrePHOX, NeoPHOX, etc)[5] they are limited in substrate and reaction scope and/or require more reaction steps.[5] The discovery of efficient

ligands prepared in only a few steps from inexpensive raw materials, easy to handle (i.e., solid, robust and air stable) and that tolerate a broad range of substrates has therefore attracted the attention of many researchers. Our group has expertise in preparing easy to handle ligand families from readily available starting materials.[6] We and others have shown the benefits of having biaryl phosphite moieties in the ligands for several asymmetric catalytic transformations.[1,6a-e] Our group has contributed with an improved generation of phosphite-N ligand libraries.[6e] In this context, we found that replacing the phosphine moiety in phosphine-oxazoline PHOX ligands by a biaryl phosphite-moiety not only improved activity but also increased substantially the substrate scope in the Pd-allylic substitution[7] and the Ir-catalyzed hydroboration[8]. The reason for this exceptional performance is the flexiblility of the biaryl phosphite group that allows the chiral pocket of the catalyst to accommodate itself according to the steric demands of the substrate.[7b] Moreover, their easy preparation from alcohols and their higher stability towards air and other oxidizing agents than other commonly used phosphines make phosphite ligands very attractive.[2,6a-e] These features facilitate preparing large series of ligands in the quest to maximize catalytic performance for each particular reaction and substrate.

Because of its perfect atom economy, operational simplicity and effectiveness, the hydrogenation of prochiral olefins is one of the most reliable asymmetric catalytic methods for the synthesis of optically active compounds.[1,9] Nowadays, a remarkable range of ligands are being applied to transform a broad range of substrates. The best results are obtained when the substrate has a good coordinating group close to the C=X bond because its chelating ability facilitates transferring the chirality from the catalyst to the product. There are, however, functionalized substrates whose asymmetric hydrogenation is still not solved. Among them cyclic β-enamides have recently attracted the attention because their reduction products are found in many pharmaceuticals and biologically active products.[10] In contrast to α-enamides, most of the catalysts for β-enamides give low enantiomeric excesses and are based on Rh and Ru-catalysts modified with diphosphine ligands.[11] A breakthrough in this area came in 2016, when Verdaguer et al. showed that Ir-P,N catalysts, which had been mainly used to reduce unfunctionalized olefins, could also reduce cyclic β-enamides derived from 2-tetralones with better enantioselectivities than the Ru/Rh-catalysts described in the literature (up to 99% ee).[12a] Just afterwards, our group showed that Ir catalysts modified with PHOX-based phosphite-oxazoline ligands **L1a-c**, **L3a-c** and **L4-L6b** (Figure 1) can also be successfully used to reduce cyclic β-enamides derived from both 2-tetralones and 3-chromanones.[12b] More recently, our group also found that P,S ligands can be also successfully applied in the hydrogenation of both, β-enamides derived from 2-aminotetralines and 3-aminochromanes with ee's up to 99%.[13] Despite these advances, the potential of P,X ligands for the hydrogenation of functionalized olefins has been overlooked. The need for easy-to-synthesize, easy-to-handle and highly efficient P,X ligands for the reduction of β-enamides derived from both, 2-tetralones and 3-chromanones continues.

Another important class of olefins are the so-called minimally functionalized olefins, that do not have an adjacent coordinative polar group.[14] The hydrogenation of minimally functionalized olefins has not reached the same level of development as the hydrogenation of functionalized olefins and its synthetic utility remains limited. Following the pioneering work of Pfaltz et al. using [Ir(cod)(PHOX)]BArF catalyst precursors,[15] research in this field has focussed in Ir-catalysts modified with chiral heterodonor P/N ligands.[16,17] However, most of the Ir-catalysts are still very sensitive to the olefin geometry as well as to the number and nature of substituents in the olefin. Many important substrates still provide suboptimal results with known catalysts. For example, Ir-phosphine-oxazoline PHOX catalysts have only been able to successfully hydrogenate a limited range of trisubstituted alkenes with E-geometry.[15,18] Our group has shown the benefits of using phosphite-oxazoline ligands for this process, which has become the state of art for the reduction of these challenging substrates.[19]

Combining Verdaguer et al.'s work and our biaryl phosphite-containing ligands, in this paper we report the family of phosphite-oxazoline ligands (**L1-L7a-g**, Figure 1) for the reduction of both, minimally functionalized olefins and cyclic β-enamides. Ligands **L1-L4** are based on privileged phosphine-oxazoline PHOX ligands in which the phosphine moiety was replaced with biaryl phosphite moieties.[20] Ligands **L5-L7** were designed to study the effect of the size of the chelate ring than has been found to influence the catalytic performance in the hydrogenation of several olefins. They differ from ligands **L1-L4** by a methylene spacer between the oxazoline and the phenyl ring of the ligand backbone.[21]

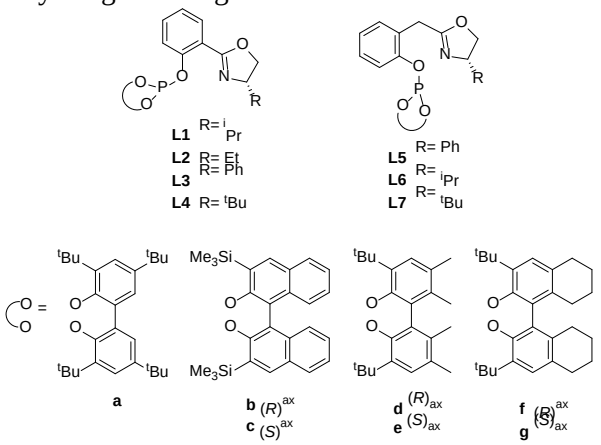


Figure 1. Phosphite-oxazoline ligands **L1-L7a-g**

Results and Discussion

Synthesis of Ir(I)- and Rh(I)-catalyst precursors

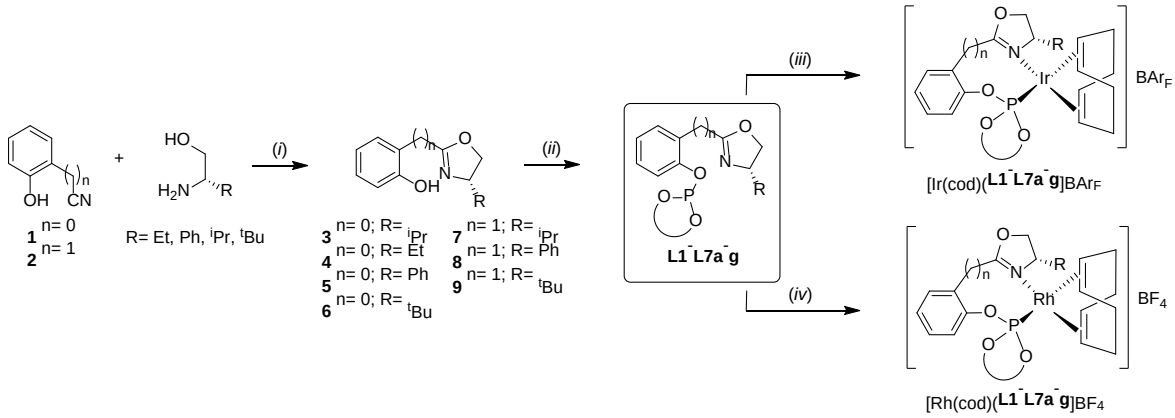
The Ir- and Rh-catalyst precursors [Ir(cod)(**L1**-**L7a**-**g**)]BAr_F and [Rh(cod)(**L1**-**L7a**-**g**)]BF_4 have been synthesized in only three steps from readily available starting materials as shown in Scheme 1. First, the coupling of hydroxyl-cyanides **1** and **2** with the appropriate amino alcohol yielded the hydroxyl-oxazolines **3**-**9** with diverse oxazoline substituents (Scheme 1, step *i*).[22] Then, condensation of the desired in situ formed phosphorochloridites $ClP(OR)_2$ $(OR)_2$= **a**-**g**) with the corresponding hydroxyl-oxazoline yielded phosphite-oxazoline ligands with several biaryl phosphite groups **L1**-**L7a**-**g**, in high yields as white solids (Scheme 1, step *ii*). Advantageously, **L1**-**L7a**-**g** are stable in air, so manipulation and storage was performed in air. In the last step of the synthesis, complexation of the ligands to [Ir(μ-Cl)(cod)]$_2$ followed by in situ Cl^-/BAr_F^- counterion exchange with $NaBAr_F$ gave access to the desired cationic Ir-catalyst precursors (Scheme 1, step *iii*). These were isolated in pure form as air-stable red-orange solids in excellent yields after simple extraction. No further purification was required. For the Rh-catalyst precursors, in the last step of the synthesis [Rh(cod)$_2$]BF_4 reacted with one equivalent of the appropriate ligand and the complexes were isolated in pure form as yellow powders by adding cold hexane (Scheme 1, step *iv*).

All ligands **L1**-**L7a**-**g** and complexes [M(cod)(**L1**-**L7a**-**g**)]X (M= Ir; X= BAr_F and M= Rh; X= BF_4) were characterized by $^{31}P\{^1H\}$, ^1H and $^{13}C\{^1H\}$ NMR spectra and mass spectrometry. All data were in agreement with assigned structures. The spectra assignments were supported by the information obtained from ^1H-^1H and ^1H-^{13}C correlation measurements. HRMS-ESI spectra showed the heaviest ions at m/z corresponding to the loss of the BAr_F anion from the molecular species for the Ir-complexes and the loss of BF_4 anion for Rh-complexes. The ^1H, ^{13}C, and ^{31}P NMR spectra showed the expected pattern for these C_1-complexes. The VT-NMR in CD_2Cl_2 (+35 to -85 °C) spectra showed only one isomer in solution. In all cases, one singlet in the ^{31}P-$\{^1H\}$ NMR spectra was observed. See Supporting Information for characterization details.

Asymmetric hydrogenation of minimally functionalized olefins

Asymmetric hydrogenation of trisubstituted olefins

The efficiency of ligands **L1**-**L7** in the hydrogenation of trisubstituted olefins with different geometry was initially evaluated with *E*-substrates **S1** (model olefin), **S2** and **S3**; and the *Z*-substrates **S4** and **S5** (Table 1). *Z*-Trisubstituted olefins are usually hydrogenated less enantioselectively than the related *E*-trisubstituted olefins. By selecting the ligand parameters we could achieve high enantioselectivities in the reduction of *E*- and *Z*-olefins (ee's up to 97% and 90%, respectively) thus overcoming one of the limitations of the parent ^{t}BuPHOX phosphine-oxazoline ligand in the reduction of *Z*-olefins (ee values up to 42% for **S4**, entry 24)[15]. In general, the enantioselectivities were found to be highly dependent on the ligand structure and the substrate type. While the best enantioselectivities for *E*-substrates were obtained with **L5b** and **L5c** that contain a methylene spacer between the oxazoline and the phenyl ring of the ligand backbone (Table 1 entries 16 and 17), for *Z*-substrates the best enantioselectivities were obtained with the ligand without the methylene spacer **L3c** (Table 1, entry 11). Moreover, the oxazoline substituents and the substituent/configuration of the biaryl phosphite group also affected the enantioselectivity. Reactions conducted with ligands containing a Ph oxazoline group proceeded with the highest enantioselectivities for both substrate types (entries 11 and 17). This is economically advantageous because the (*S*)-phenylglycinol used in the preparation of **L5** is the cheapest of the amino alcohols employed (up to eight times cheaper than *tert*-leucinol that is used in **L4** and **L7** as well as in other state-of-the-art oxazoline-based



Scheme 1. Synthesis of phosphite-oxazoline ligands **L1**-**L7a**-**g** and the corresponding Ir- and Rh-catalyst precursors. (*i*) $ZnCl_2$, toluene or chlorobenzene at reflux for 18-72 h (yields 62-79%). (*ii*) $ClP(OR)_2$ $(OR)_2$= **a**-**g**, Py, toluene at rt for 18 h (yields 40-80%). (*iii*) [Ir(μ-Cl)(cod)]$_2$, CH_2Cl_2 at 40ºC for 60 min then H_2O, $NaBAr_F$ at rt for 30 min (yields 91-96%). (*iv*) [Rh(cod)$_2$]BF_4, CH_2Cl_2 at rt for 60 min then precipitated with cold hexane (yields 88-93%).

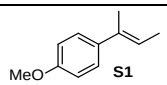
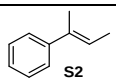
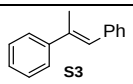
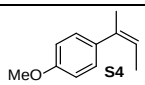
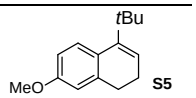
ligands such as the ^{t}BuPHOX phosphine-oxazoline ligand). Additionally, whereas for the more demanding *Z*-substrates the best enantioselectivity is obtained with **L3c**, which contains an *S* binaphthyl group **c** (entry 11), for *E*-substrates the best enantioselectivities were obtained with either *S* or *R* binaphthyl groups (**b** and **c**; entries 16 and 17). From these latter results we can conclude that both enantiomers of the hydrogenated *E*-substrates can be obtained in high enantioselectivities by simply switching the configuration of the biaryl phosphite group in ligands **L5**.

We also studied these reactions at a low catalyst loading (0.25 mol%) with ligands **L3c** and **L5b-c**, which had provided the best results so far. The high enantioselectivities were retained (Table 1, entries 25-26). We also tested 1,2-propylene carbonate (PC) as a solvent. PC has emerged as an environmentally friendly alternative to standard organic solvents because of its high boiling point, low toxicity, and "green" synthesis.[23] Using PC we repeated the hydrogenation of substrates **S1**−**S5** with the ligands that provided the best enantioselectivities (Table 1, entries 28-30). We were pleased to see no loss of enantioselectivity.

Remarkably, we could also achieve high enantioselectivity in the hydrogenation of the challenging exocyclic benzofused five-membered olefin **S6** with Ir/**L1g** (Table 2, entry 1). Chiral benzofused five-membered alkanes are key structural elements in several natural and bioactive molecules.[24] It should be noted that the hydrogenation of this type of olefins is not achieved using the parent phosphine-oxazoline ^{t}Bu-PHOX ligand (conversions below 5%)[16z] and that only Ir/In-BiphPHOX has been recently reported to successfully reduce this type of substrate.[16z]

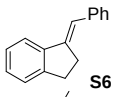
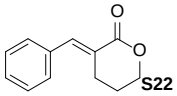
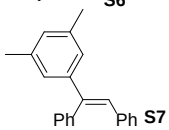
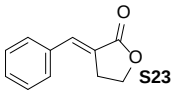
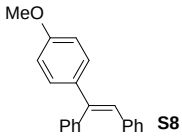
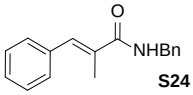
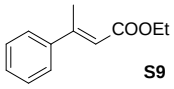
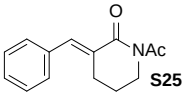
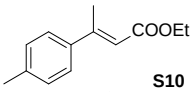
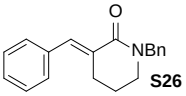
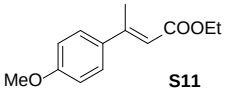
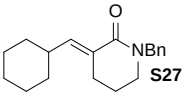
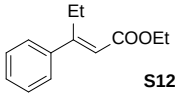
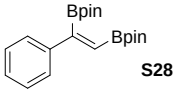
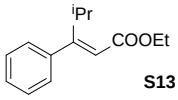
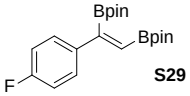
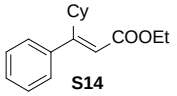
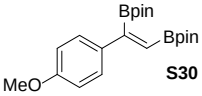
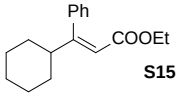
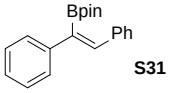
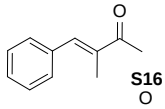
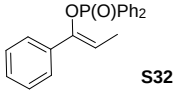
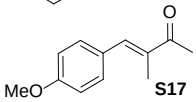
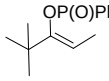
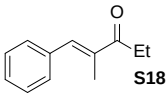
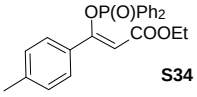
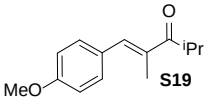
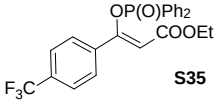
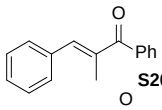
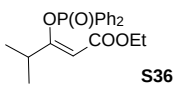
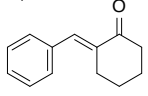
High enantioselectivities (up to 97%, Table 2, entries 2-3) were also obtained in the reduction of substrates **S7-S8** with the Ir/**L5b** system. Triaryl-substituted substrates have been scarcely studied,[16p,17c,19e]

Table 1. Ir-catalyzed hydrogenation of *E*- and *Z*-subtrates **S1**-**S5** using ligands **L1**-**L7a**-**g**[a]

		 S1	 S2	 S3	 S4	 S5
Entry	**L**	% ee[b]	% ee[b]	% ee[b]	% ee[b]	% ee[b]
1	**L1a**	72 (*R*)	72 (*R*)	78 (*R*)	86 (*S*)	51 (*S*)
2	**L1b**	78 (*R*)	68 (*R*)	74 (*R*)	30 (*S*)	7 (*R*)
3	**L1c**	61 (*R*)	58 (*R*)	63 (*R*)	85 (*S*)	81 (*S*)
4	**L1d**	25 (*R*)	21 (*R*)	24 (*R*)	15 (*S*)	14 (*R*)
5	**L1e**	55 (*R*)	59 (*R*)	56 (*R*)	72 (*S*)	83 (*S*)
6	**L1f**	29 (*R*)	31 (*R*)	34 (*R*)	0	4 (*R*)
7	**L1g**	58 (*R*)	54 (*R*)	61 (*R*)	90 (*S*)	87 (*S*)
8	**L2a**	9 (*R*)	11 (*R*)	7 (*R*)	47 (*S*)	41 (*S*)
9	**L3a**	0	6 (*R*)	4 (*R*)	60 (*S*)	64 (*S*)
10	**L3b**	40 (*R*)	35 (*R*)	43 (*R*)	78 (*R*)	81 (*R*)
11	**L3c**	15 (*S*)	22 (*S*)	19 (*S*)	91 (*S*)	89 (S)
12	**L4a**	72 (*R*)	73 (*R*)	74 (*R*)	88 (*S*)	71 (*S*)
13	**L4b**	19 (*R*)	17 (*R*)	21 (*R*)	17 (*S*)	3 (*R*)
14	**L4c**	44 (*R*)	46 (*R*)	45 (*R*)	84 (*S*)	75 (*S*)
15	**L5a**	15 (*R*)	11 (*R*)	14 (*R*)	5 (*S*)	6 (*R*)
16	**L5b**	94 (*R*)	94 (*R*)	96 (*R*)	17 (*R*)	48 (*R*)
17	**L5c**	95 (*S*)	96 (*S*)	97 (*S*)	3 (*S*)	51 (*R*)
18	**L6a**	81 (*R*)	78 (*R*)	84 (*R*)	56 (*S*)	31 (*R*)
19	**L6b**	92 (*R*)	91 (*R*)	93 (*R*)	3 (*R*)	40 (*S*)
20	**L6c**	65 (*S*)	69 (*S*)	68 (*S*)	45 (*S*)	31 (*R*)
21	**L7a**	76 (*R*)	71 (*R*)	72 (*R*)	56 (*S*)	87 (*S*)
22	**L7b**	23 (*R*)	24 (*R*)	28 (*R*)	24 (*S*)	69 (*S*)
23	**L7c**	0	4 (*S*)	8 (*S*)	51 (*S*)	28 (*R*)
24[c]	**^{t}BuPHOX**	61 (*R*)	-[d]	97 (*R*)	42 (*S*)	-[d]
25[e]	**L3c**	14 (*S*)	21 (*S*)	19 (*S*)	91 (*S*)	88 (S)
26[e]	**L5b**	94 (*R*)	94 (*R*)	96 (*R*)	16 (*R*)	48 (*R*)
27[e]	**L5c**	95 (*S*)	96 (*S*)	97 (*S*)	3 (*S*)	51 (*R*)
28[f]	**L3c**	13 (*S*)	20 (*S*)	21 (*S*)	91 (*S*)	89 (S)
29[f]	**L5b**	93 (*R*)	94 (*R*)	96 (*R*)	14 (*R*)	46 (*R*)
30[f]	**L5c**	95 (*S*)	95 (*S*)	96 (*S*)	6 (*S*)	54 (*R*)

[a] Reactions carried out at room temperature by using 0.5 mmol of substrate and 1 mol% of Ir-catalyst precursor at 50 bar of H_2 using dichloromethane (2 mL) as solvent. Otherwise noted, full conversions were achieved after 2 h.[b] Enantiomeric excesses measured by chiral GC or HPLC. [c] Data from ref. [15]. [d] Data not reported. [e] Reactions carried out at 0.25 mol% of Ir-catalyst precursor at 50 bar of H_2. Full conversions were achieved after 6 h. [f] Reactions carried out using PC as solvent and 1 mol% of Ir-catalyst precursor at 100 bar of H_2. Full conversions were achieved after 12 h.

Table 2. Selected results for the hydrogenation of trisubstituted olefins **S6**-**S36** using [Ir(cod)(**L1**-**L7a**-**g**)]BAr_F catalyst precursors.[a]

Entry	Substrate	L	% Conv[b]	% ee[c]	Entry	Substrate	L	% Conv[b]	% ee[c]
1	 **S6**	**L1g**	100	91 (*R*)	17[d]	 **S22**	**L5c**	81	>99 (*R*)
2	 **S7**	**L5b**	95	97 (-)	18[d]	 **S23**	**L5c**	49	99 (*R*)
3	 **S8**	**L5b**	99	99 (-)	19[d]	 **S24**	**L5c**	100	>99 (*R*)
4	 **S9**	**L3a**	100	98 (*R*)	20[d]	 **S25**	**L5c**	72	>99 (*R*)
5	 **S10**	**L3a**	100	98 (*R*)	21[d]	 **S26**	**L5c**	100	>99 (*R*)
6	 **S11**	**L3a**	100	99 (*R*)	22[d]	 **S27**	**L5c**	100	>99 (*R*)
7	 **S12**	**L3a**	100	99 (*R*)	23	 **S28**	**L5c**	100	>99 (*S*)
8	 **S13**	**L3a**	100	99 (*R*)	24	 **S29**	**L5c**	100	99 (*S*)
9	 **S14**	**L3a**	100	99 (*R*)	25	 **S30**	**L5c**	100	99 (*S*)
10	 **S15**	**L3a**	100	93 (*R*)	26[d]	 **S31**	**L5b**	70	>99 (*S*)
11	 **S16**	**L5c**	100	96 (*R*)	27[d]	 **S32**	**L5b**	70	95 (*R*)
12	 **S17**	**L5c**	100	96 (*R*)	28[d]	 **S33**	**L5b**	67	96 (*R*)
13	 **S18**	**L5c**	100	96 (*R*)	29	 **S34**	**L5b**	51	94 (*R*)
14	 **S19**	**L5c**	100	96 (*R*)	30[d]	 **S35**	**L5b**	48	95 (*R*)
15	 **S20**	**L5c**	100	97 (*R*)	31[d]	 **S36**	**L5b**	43	96 (*R*)
16	 **S21**	**L5c**	100	96 (*R*)					

[a] Reaction conditions: 2 mol % catalyst precursor, CH_2Cl_2 as solvent, 50 bar H_2, 4 h. [b] Conversion measured by ^{1}H-NMR after 2 h. [c] Enantiomeric excesses measured by chiral GC or HPLC. [d] Reactions carried out during 24 h.

although their hydrogenation is a sustainable and straightforward method to achieve diarylmethine chiral centers.[25]

We then moved towards the reduction of key trisubstituted substrates with poorly coordinative groups. Their hydrogenation is of interest because they can be further functionalized and become key intermediates for more complex chiral molecules. The results are shown in Table 2 (for a complete series of results, see Table SI-1 in the Supporting Information). We found that, again, the parameters of the ligands must be optimized for each substrate if enantioselectivities are to be high. We first hydrogenated a large series α,β-unsaturated esters **S9**-**S15** (Table 2, entries 4-10), with different electronic properties in the phenyl ring (**S9**-**S11**) and with different steric properties of the alkyl substituents (**S9**, **S12**-**S14**). The hydrogenation of these substrates provides a simple entry point to chiral carboxylic ester derivatives, which are found in relevant products.[26] For all of them enantioselectivities (ee's up to 99%) were excellent and comparable to the best reported to date. It should be highlighted the 93% ee obtained for the more demanding *Z*-isomer **S15** (entry 10). The effect of the ligand parameters on enantioselectivity is different than for previous **S1**-**S8** substrates. The best enantioselectivities were obtained with ligand **L3a**, which maintains the economic benefits of a Ph oxazoline substituent but with the added advantage that an achiral inexpensive 3,3',5,5'-tetra-*tert*-butyl-[1,1'-biphenyl]-2,2'-diyl phosphite moiety (**a**) can be used. With the Ir/**L5c** catalytic system we were also able to hydrogenate α,β-unsaturated enones **S16**-**S21** with results (ee's up to 98%; Table 2, entries 11-16) comparable to the best enantioselectivities previously reported.[27,28] Interestingly, Ir/**L5c** provided similar high enantioselectivities irrespective of the nature of the alkyl substituent and the electronic nature of the substrate phenyl ring. Being able to hydrogenate such a wide range of α,β-unsaturated enones is highly significant since the obtained ketones are found in many relevant products. Despite their importance, they have been less studied and less successfully hydrogenated than other trisubstituted olefins with poorly coordinative polar groups.[27] Other difficult substrates such as α,β-unsaturated δ- and γ-lactones **S22**-**S23** (entries 17 and 18), acyclic amide **S24** (entry 19) and δ-lactams **S25**-**S27** (entries 20-22) were also successfully reduced with the Ir/**L5c** system (ee's up to >99%). Chiral amides with stereogenic centres in the α-position and δ- and γ-lactones/lactams are common in a variety of natural products as well as useful building blocks in synthetic chemistry (*i.e.* amide group can be easily transformed into other useful compounds such as amines). Despite their relevance, very few successful examples of Ir-catalysts can be found in the literature and they have a limited substrate scope.[29]

Alkenylboronic esters and enol phosphinates are two other relevant sets of substrates that are receiving much attention. The asymmetric reduction of alkenylboronic esters will open up a new straightforward and sustainable route for preparing enantiomerically pure organoboron compounds. Chiral organoboron compounds are interesting because the boronate group can undergo stereospecific transformations to form C-N, C-O and C-C bonds. On the other hand, the effective hydrogenation of enol phosphinates opens up an appealing route for obtaining chiral organophosphinates, which can be easily transformed into high value compounds such as alcohols and phosphines. Despite the importance of hydrogenating alkenylboronic esters and enol phosphinates, only a few reports have been published and show a limited success.[30] In this context, it was noteworthy that by modifying the ligand parameters we could reach high enantioselectivities for alkenylboronic esters **S28**-**S31** (Table 2, entries 23-26) and enol phosphinates **S32**-**S36** (Table 2, entries 27-31). In the reduction of alkenylboronic esters, the highest enantioselectivities (up to 99%) were achieved using [Ir(cod)(**L5c**)]BAr_F, while for enol phosphinates the best enantioselectivities (ee's up to 96%) were obtained with [Ir(cod)(**L5b**)]BAr_F.

In summary, the simple substitution of the phosphine by a phosphite group and/or the introduction of a methylene spacer between the oxazoline and the phenyl ring of the ligand backbone in phosphine-oxazoline ^{t}BuPHOX ligand extended the range of trisubstituted olefins that could be successfully hydrogenated with enantioselectivities that were among the best reported so far.[14h] In addition, the ligands that provided the best enantioselectivities contained the Ph substituent in the oxazoline moiety instead of the pricy ^{t}Bu substituent.

Asymmetric hydrogenation of disubstituted olefins

To further study the potential of the **L1**-**L7a-g** ligands, we screened them in the Ir-catalyzed hydrogenation of 1,1-disubstituted substrates. Enantioselectivity is more difficult to control in these substrates than in trisubstituted olefins. Most catalysts fail either to control the face-selective coordination of the less hindered disubstituted substrate or to suppress the isomerization of the olefin that leads to the formation of the more stable *E*-trisubstituted substrates, which in turn form the opposite enantiomer when hydrogenated.[14e]

As a model substrate we chose the 3,3-dimethyl-2-phenyl-1-butene **S37**. The results are summarized in Table SI-2 in the Supporting Information. The best enantioselectivity (ee's up to 98%), comparable to the best one reported in the literature, was obtained with **L3a** (Figure 2). This ligand has the economic benefits of both a Ph oxazoline substituent and an achiral biaryl phosphite moiety **a**. The introduction of a methylene spacer between the oxazoline and the phenyl ring of the ligand backbone did not improve the enantioselectivity.

We next studied the asymmetric hydrogenation of other terminal disubstituted olefins (Figure 2; for a complete series of results, see Table SI-3 in the Supporting Information). We noted that **Ir/L3a** easily

tolerates variations in the electronic and steric properties of the substituents in the aryl moiety of the substrate. A broad range of terminal olefins (**S38**-**S44**) were reduced in high enantioselectivities comparable to **S37**. For **S43** and **S44** with *ortho* substituents, longer reaction times were required to achieve full conversions.

Among the results, it is worth mentioning that the hydrogenation of α-alkylstyrenes bearing decreasingly sterically demanding alkyl substituents (**S45**-**S48**) proceeded with somewhat lower enantioselectivities (from 83% to 91%). Nevertheless, we found that enantioselectivities for these substrates could be maximized by choosing the ligand parameters. A plausible explanation for the lower enantioselectivity can be either that hydrogenation competes with isomerization or that face selectivity problems occur. To clarify this aspect, we run deuterium labeling experiments (Scheme 2) in which we hydrogenated **S1** and **S48** with deuterium with Ir/**L1b** and Ir/**L6b** catalyst precursors.

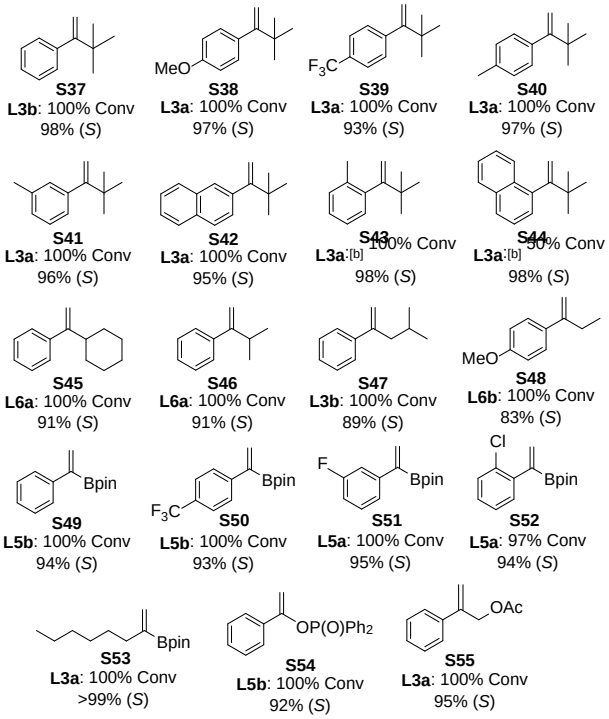
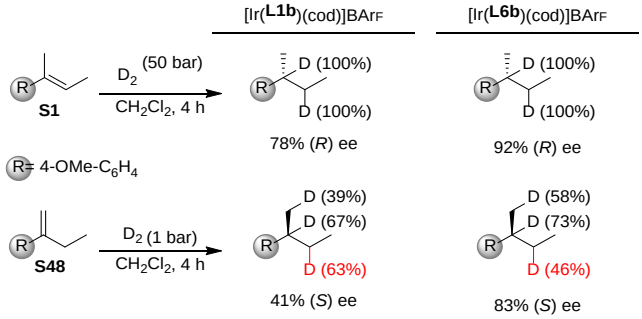


Figure 2. Selected results for the hydrogenation of disubstituted olefins **S37**-**S55** using [Ir(cod)(**L1**-**L7a**-**g**)]BAr_F catalyst precursors. Reaction conditions: 1 mol % catalyst precursor, CH_2Cl_2 as solvent, 1 bar H_2, 4 h. [b] Reaction carried out for 12 h.

In contrast to **S1**, the reduction of **S48** led to the addition of deuterium not only at the double bond (as expected) but also at the allylic position. This agrees with the existence of a competing isomerization pathway. [31] This was supported by the mass spectra of the corresponding deuterated product from **S48** showing species with more than two deuterium atoms. In line with this, the Ir/**L6b** system shows less deuterium atoms incorporated at the allylic position than the Ir/**L1b**. This indicates that Ir/**L6b** controls better the isomerization than Ir/**L1b**, which agrees with the higher enantioselectivity observed with Ir/**L6b**. Although in olefins prone to isomerization (**S45**-**S48**) this competing reaction was not completely suppressed, the introduction of a biaryl phosphite group together with the combination of the right ligand parameters minimized this side reaction to achieve ee's comparable to the best ones reported. Besides, by introducing the biaryl phosphite moiety, the face coordination mode was successfully controlled thus facilitating the reduction of a broad range of 1,1-disubstituted substrates.



Scheme 2. Deuterium labeling experiments of substrates **S1** and **S48** using Ir/**L1b** and Ir/**L6b** catalyst precursors. The percentage of incorporation of deuterium atoms is shown in brackets. The results of the indirect addition of deuterium due to the isomerization process are shown in red.

Finally, due to the relevance of olefins with poorly coordinative groups, we wanted to see if the excellent catalytic performance in the reduction of the trisubstituted enol phosphinates and alkenylboronic esters was maintained for the even more challenging terminal analogues. We were able to obtain high-to-excellent enantioselectivities (ee's up to 99%) in the reduction of substrates **S49**-**S54** (Figure 2). The results are among the best in the literature for each substrate, even in the reduction of highly appealing substrates such as pinacolatoboron-containing substrates **S49**-**S53**[32] and enol phosphinate **S54**[33] for which only very few catalytic systems have provided high enantioselectivities. The successful reduction of aryl-substituted boronic esters **S49**-**S52** is a relevant finding that overcomes the results reported in the literature in the hydrogenation of this type of substrates and nicely complements the current state of the art. It is also noteworthy that although **S53** is prone to isomerization, it was hydrogenated with excellent enantioselectivity. Similarly, the hydrogenation of the allylic acetate **S55**[34] also proceeded with high activity and enantioselectivity with catalyst Ir-**L3a**. Derivatives of the hydrogenation product of **S55** are used as components of fragrance mixtures (i.e., Pamplefleur) and also as intermediates for the synthesis of natural products and drugs (i.e., modulators of dopamine D3 receptors).[35]

To summarize, the results for the asymmetric hydrogenation of disubstituted olefins are among the

best reported for this type of challenging substrates and overcome one of the limitations of the parent phosphine-oxazoline ^{t}BuPHOX ligand, which was unable to reduce the 1,1-disubstituted substrate class with high enantioselectivities.

Asymmetric hydrogenation of cyclic β-enamides

We finally turned our attention to the asymmetric reduction of challenging β-enamides. 2-Aminotetralines and 3-aminochromanes are key structural units in many therapeutic agents and biologically active natural products (Figure 3).[10]

The asymmetric hydrogenation of β-enamides will open up a direct, atom-efficient, path to synthesize these compounds. So far, only few successful examples can be found in the literature and they are limited in substrate scope. In contrast to the α-enamides, most of the catalysts for β-enamides provide low enantiomeric excesses and are based on Rh and Ru-catalysts.[11] Among the most successful reports, Ratovelomanana et al. published the synthesis of 3-aminochromanes with enantioselectivities up to 96% using Ru-diphosphine catalysts.[11f] A more recent report showed similar high enantioselectivities in the reduction of enamides derived from 2-tetralones (ee's up to 96%) and enamides derived from 3-chromanones (ee's in the range 94-98%), using a Rh-diphosphine catalysts.[11k] They needed, however, to use WingPhos, a P-stereogenic diphosphine ligand synthesized in nine steps.

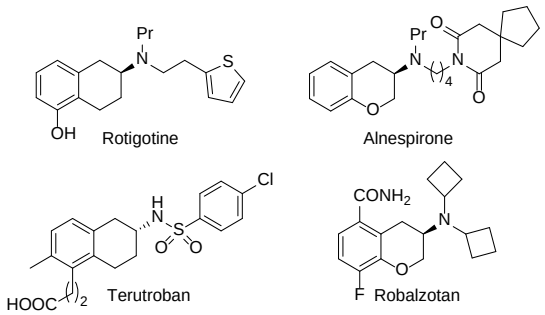


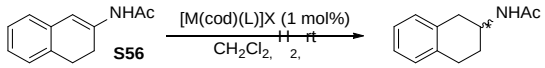
Figure 3. Examples of chiral 2-aminotetralines and 3-aminochromanes with pharmaceutical applications

In 2016, two reports showed that Ir-P,N catalysts, that have been mainly used to reduce unfunctionalized olefins, are also able to reduce cyclic β-enamides.[12] In this respect, we identified that Ir-catalysts modified with the simple PHOX-based phosphite-oxazoline **L1a-c**, **L3a-c** and **L4**-**L6b** can be successfully used to reduce cyclic β-enamides derived from 2-tetralones and 3-chromanones.[12b] Our preliminary results (at 50 bar of H_2 at room temperature using 1 mol% of the corresponding [Ir(cod)(**L**)]BAr_F catalyst precursors) showed that ligands with a methylene spacer between the oxazoline and the phenyl ring provided higher enantioselectivities than ligands without this methylene moiety. We also found that a chiral *R*-binaphthyl moiety **b** was needed for high enantioselectivities.[12b]

Therefore, and in order to further improve enantioselectivities, in this work we expanded our previous study to other phosphite containing-PHOX based ligands with a methylene spacer. Thus, we tested the new ligands containing a ^{t}Bu oxazoline moiety (ligands **L7**) and those incorporating other *R*-configured biaryl phosphite moieties (ligands **L5**-**L7c**,**d**,**f**). For comparison we also tested the new ligands **L1**-**L4d**,**f** that contain the *R*-biaryl phosphite moieties **d** and **f** but not the methylene spacer. See Table 3 for selected results (for a complete series of results, see Table SI-4 in the Supporting Information). Neither these new chiral biaryl phosphite groups nor the ^{t}Bu oxazoline moiety improved the previous enantioselectivities. Indeed the presence of the ^{t}Bu oxazoline group lowered both activity and enantioselectivity. The use of the new ligands with other *R*-biaryl phosphite moieties (**d**, **f**) provide the same enantioselectivities than the best ones obtained with ligands **L5**-**L6b**. Therefore, ligands **L5b** and **L6b**,**d**,**f** provided the reduced product in full conversion and 98% of ee (Table 3).

More recently, our group also found for the first time that with P-thioether ligands both enantiomers of the hydrogenated can been obtained by switching from Ir to Rh.[13] Therefore, in this paper we also extended the use of ligands **L1**-**L7** in the Rh-catalyzed hydrogenation of β-enamides. For comparison, we firstly evaluated ligands **L1**-**L7** in the Rh-catalyzed hydrogenation of the model *N*-(3,4-dihydronaphthalen-2-yl)acetamide **S56** substrate. The selected results are shown in Table 3 (for complete series of results see Table SI-4 in the Supporting Information). We used the same optimal reaction conditions found in our previous study with Rh-P,S catalytic systems in the reduction of cyclic β-enamides. The reactions were therefore performed in dichloromethane using 1 mol% of the catalyst loading under 30 bar of H_2. The catalysts were prepared in situ by adding the appropriate ligand to the $[Rh(cod)_2]BF_4$ catalyst precursor. Again the methylene spacer between the oxazoline and the phenyl ring affected positively the enantioselectivity while the presence of a ^{t}Bu oxazoline group affected negatively. The effect of the methylene spacer is more significant in Rh-catalysts than in Ir-catalysts. As previously observed with Ir-catalysts, the results also indicated that the ligand backbone is not able to control the tropoisomerism of the biphenyl phosphite moiety (**a**). Therefore the chiral *R*-biaryl phosphite moieties are needed to maximize enantioselectivities and activities. However, in contrast to Ir-catalysts, the presence of the corresponding chiral *S*-biaryl phosphite moiety also provided quite good enantioselectivities. In summary, the best enantioselectivities of up to 94% ee were therefore obtained with ligands **L5b** and **L6b**,**d**,**f**. Advantageously, we also found that both enantiomers of the hydrogenated products could be reached with the same ligand by simple exchanging Ir to Rh (Table 3).

Table 3. Selected results for the reversal of enantioselectivity observed in the Ir- and Rh-catalyzed hydrogenation of **S56** [a]



		[Ir(cod)(**L**)]BAr_F		[$Rh(cod)_2$]BF_4/**L**	
Entry	**L**	%Conv[b]	%ee[c]	%Conv[b]	%ee[c]
11	**L5b**	100	98 (*S*)[d]	100	94 (*R*)
13	**L6b**	100	98 (*S*)[d]	100	94 (*R*)
14	**L6d**	100	98 (*S*)	100	93 (*R*)
15	**L6f**	100	98 (*S*)	100	94 (*R*)

[a] Reactions carried out using 0.5 mmol of substrate, 1 mol% of catalyst precursor using dichloromethane (2 mL) as solvent and at room temperature and 50 bar of H_2 for Ir-catalysts or at 5 °C and 30 bar of H_2 for Rh-catalysts. [b] Conversion measured by ^{1}H-NMR after 20 h for Ir-catalysts and 36 h for Rh-catalysts. [c] Enantiomeric excess determined by HPLC. [d] Data from ref [12b].

We then evaluated the effect of several reaction parameters on catalytic performance (see Table SI-5 in the Supporting Information). We were pleased to find that full conversions and high enantioselectivities can be maintained by lowering the pressure of H_2 to 10 bar. We also found that the catalytic performance is unaffected when using either the in situ formed or the preformed catalyst precursor [Rh(cod)(**L**)]BF_4. In the optimal reaction conditions we then evaluated the substrate scope with other cyclic β-enamides. Figure 4 shows the results using Rh/**L6d** catalyst as example (for a complete series of results, see Table SI-3 in the Supporting Information). For comparison, Figure 4 also collects the results with the corresponding Ir-catalyst.

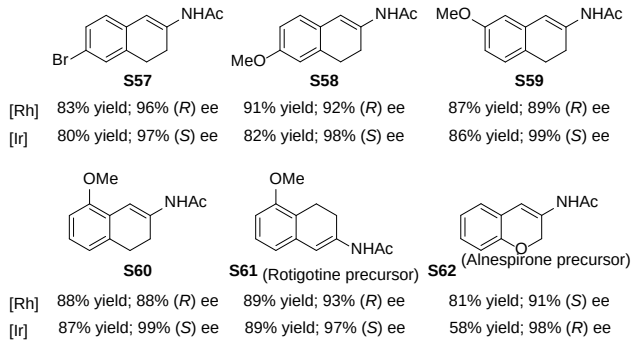
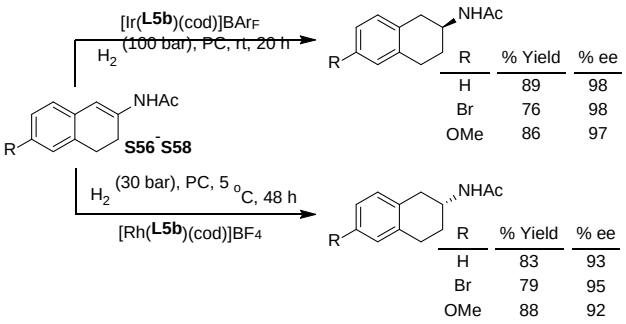


Figure 4. Asymmetric Rh-catalyzed hydrogenation of cyclic β-enamides **S57**-**S62** using [Rh(cod)(**L6d**)]BF_4. Reactions conditions: catalyst precursor (1 mol%), substrate (0.5 mmol), CH_2Cl_2 (2 mL), 10 bar H_2, 5 °C, 50 h. For comparative purposes the results achieved with related Ir-**L6d** catalytic system (1 mol%) using 50 bar of H_2 are also included.

A range of substituted cyclic enamides derived from β-tetralones (**S57**-**S61**), that contemplate all possible variations in the substitution pattern of the 3,4-dihydronaphthalene core were hydrogenated with high enantioselectivities comparable to the best one reported (ee's up to 96%). Also, the replacement of the metal gave access again to both enantiomers of the reduced products with high enantioselectivities. Finally, we were pleased to find that we could also effectively hydrogenate the enamide derived from 3-chromanone, **S62**, in high enantioselectivities and yields (ee's up to 91%).

In summary, by simply choosing the metal center, we have been able to obtain both reduced enantiomers for a broad range of cyclic β-enamides in enantioselectivities comparable to the best one reported under mild reaction conditions. Again the ligand that contains the phenyl substituent at the oxazoline instead of the pricy *t*-Bu has provided excellent enantioselectivities.

Finally, we went one step further and evaluated this novel set of catalysts in the M-catalyzed (M= Rh and Ir) hydrogenation of cyclic β-enamides **S56**-**S58** using 1,2-propylene carbonate. The enantioselectivities in both enantiomers of the hydrogenated products remained as high as those achieved with dichloromethane (Scheme 3).



Scheme 3. Asymmetric hydrogenation of cyclic β-enamides **S56**-**S58** using 1,2-propylene carbonate (PC). Reactions carried out using 0.5 mmol of substrate, 1 mol% of catalyst precursor using PC (2 mL) as solvent.

Conclusions

We have identified readily accessible Ir- and Rh-phosphite/oxazoline PHOX-based catalytic systems that can hydrogenate, for the first time, both a broad range of minimally functionalized and functionalized olefins (62 examples in total) in high enantioselectivities (ee's up to >99%) and conversions . Starting from privileged PHOX ligands, the phosphine moiety was replaced by a biaryl phosphite group and, in some cases, a methylene spacer was introduced between the oxazoline and the phenyl ring. With these simple modifications, the phosphite-based ligands not only had a more modular design than the source phosphine-oxazoline PHOX, but also were air-stable solids with no increase in the number of synthetic steps. With a careful selection of the ligand components, the new ligands were superior to the privileged phosphine-oxazoline PHOX ligands in the metal catalyzed

hydrogenation of challenging olefins, with enantioselectivities comparable to the best one reported. Therefore, these ligands improved the enantioselectivities achieved for challenging minimally functionalized *Z*-olefins and 1,1-disubstituted olefins, and expanded their use to olefins containing other challenging scaffolds (e.g., exocyclic benzofused and triaryl substituted olefins), olefins with poorly coordinative groups (e.g., α,β unsaturated lactams, lactones, alkenylboronic esters, ...) and cyclic β-enamides that have a fully coordinative group. Interestingly, in the Ir-hydrogenation of minimally functionalized olefins, the sense of enantioselectivity was mainly controlled by the configuration of the biaryl phosphite moiety so both enantiomers of the hydrogenated product can be obtained with the same ligand scaffold. In the hydrogenation of cyclic β-enamides, both enantiomers of the corresponding 2-aminotetralines and 3-aminochromanes could also be obtained with the same ligand by simply changing the metal from Ir to Rh. Another advantage of the new ligands over the PHOX ligands is that the best ligands are derived from affordable (*S*)-phenylglycinol rather than from expensive (*S*)-*tert*-leucinol. This latter fact together with the small number of synthetic steps (only 2) to obtain the ligands, the modularity and air-stability, and the evidence that the new Ir- and Rh-catalyst precursors maintain their enantioselectivities with environmentally friendly propylene carbonate as solvent makes them very appealing for industrial applications.

Experimental Section

General considerations

All reactions were carried out using standard Schlenk techniques under an atmosphere of argon. Solvents were purified and dried by standard procedures. All reagents were used as received. ^{1}H, $^{13}C\{^{1}H\}$ and $^{31}P\{^{1}H\}$ NMR spectra were recorded using a Varian Mercury-400 MHz spectrometer. Chemical shifts are relative to that of $SiMe_4$ (^{1}H and $^{13}C\{^{1}H\}$) as an internal standard or H_3PO_4 (^{31}P) as an external standard. ^{1}H and ^{13}C assignments were made on the basis of ^{1}H-^{1}H gCOSY and ^{1}H-^{13}C gHSQC experiments. Phosphorochloridites were easily prepared in one step from the corresponding biaryl alcohols.[36] Compounds **2**,[22b] **3-6**,[22a] **7-8**;[12b] ligands **L1-L4a**,[7a] **L1b-L1c**,[12b] **L1f-g**,[7b] and **L3-L6b**;[12 b] and complexes [Ir(cod)(**L**)]BAr_F (**L**= **L1a-c**, **L3a-c** and **L4-L6b**)[12 b] were prepared as previously described.

Typical procedure for the preparation of phosphite-oxazoline ligands

To a solution of *in situ* generated phosphochloridite (1.1 mmol) in dry toluene (6 mL), pyridine (0.16 mL, 2.0 mmol) was added. Then, this solution was placed in a -78 ºC bath. After 2 min at that temperature, a solution of the alcohol-oxazoline (1.0 mmol) and pyridine (0.16 mL, 2.0 mmol) in toluene (6 mL) was added dropwise at -78 °C. The mixture was left to warm to room temperature and stirred overnight at this temperature. The precipitate formed was filtered under argon and the solvent was evaporated under vacuum. The residue was purified by flash chromatography (under argon, using neutral alumina and dry toluene (1% NEt_3) as eluent system) to afford the corresponding phosphite-oxazoline as white solids (see Supporting Information for characterization details).

General procedure for the preparation of catalyst precursors [Ir(cod)(L1-L7a-g)]BAr_F.

The corresponding ligand (0.037 mmol) was dissolved in CH_2Cl_2 (2 mL) and $[Ir(\mu\text{-}Cl)(cod)]_2$ (12.5 mg, 0.0185 mmol) was added. The reaction mixture was refluxed at 50 ºC for 1 hour. After 5 min at room temperature, $NaBAr_F$ (38.6 mg, 0.041 mmol) and water (2 mL) were added and the reaction mixture was stirred vigorously for 30 min at room temperature. The phases were separated and the aqueous phase was extracted twice with CH_2Cl_2. The combined organic phases were dried with $MgSO_4$, filtered through a plug of celite and the solvent was evaporated to give the product as red-orange solids (see Supporting Information for characterization details).

General procedure for the preparation of catalyst precursors [Rh(cod)(L1-L7a-g)]BF_4.

The corresponding ligand (0.05 mmol) was dissolved in CH_2Cl_2 (2 mL) and $[Rh(cod)_2]BF_4$ (20.3 mg, 0.05 mmol) was added. The reaction mixture was stirred at room temperature for 1 hour. Then the solvent was partially evaporated and the desired complex was precipitated by adding cold hexane (3 mL). The precipitate was filtered off, washed twice with cold hexane (2 mL) and dried to afford the product as a yellow solid (see Supporting Information for characterization details).

Typical procedure for the Ir-catalyzed hydrogenation of minimally functionalized olefins S1-S55.

The alkene (0.5 mmol) and Ir complex (0.25-2 mol %) were dissolved in the corresponding solvent CH_2Cl_2 or PC (2 mL) and placed in a high-pressure autoclave. The autoclave was purged 4 times with hydrogen. Then, it was pressurized at the desired pressure. After the desired reaction time, the autoclave was depressurized and the solvent evaporated off. The residue was dissolved in Et_2O (1.5 ml) and filtered through a short plug of celite. The enantiomeric excess was determined by chiral GC or chiral HPLC and conversions were determined by ^{1}H NMR. The enantiomeric excesses of hydrogenated products from **S1-S55** were determined using the conditions previously described (see Supporting Information for details).

Typical procedure for the metal-catalyzed hydrogenation of cyclic β-enamides S56-S62.

The enamide (0.25 mmol) and the corresponding catalyst precursor [M(cod)(**L**)]X (M= Rh, X= BF_4 or M= Ir, X= BAr_F; 1 mol%) were dissolved in in the corresponding solvent CH_2Cl_2 or PC (1 mL) and placed in a high-pressure autoclave, which was purged four times with hydrogen. It was then pressurized at the desired pressure. After the desired reaction time, the autoclave was depressurized and the solvent evaporated off. The residue was dissolved in Et_2O (1.5 ml) and filtered through a short celite plug. Conversions were determined by ^{1}H NMR. The enantiomeric excesses of hydrogenated products were determined using the conditions previously described (see Supporting Information for details).

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References

[1] a) *Asymmetric Catalysis in Industrial Scale: Challenges, Approaches and Solutions*, 2nd ed; Eds. H.-U. Blaser, H.-J. Federsel; Wiley: Weinheim, **2010**; b) *Catalytic Asymmetric Synthesis*, 3rd ed; Ed. I. Ojima; John Wiley & Sons, Inc.: Hoboken, **2010**; c) *Comprehensive Asymmetric Catalysis*; Eds. E. N. Jacobsen, A. Pfaltz, H. Yamamoto; Springer-Verlag: Berlin, **1999**; d) *Asymmetric Catalysis in Organic Synthesis*; Ed. R. Noyori; Wiley: New York, **1994**.

[2] *Phosphorus Ligands in Asymmetric Catalysis*; Ed. A. Börner: Wiley-VCH, Weinheim, **2008**

[3] a) T. P. Yoon, E. N. Jacobsen, *Science*, **2003**, *299*, 1691-1693; b) *Privileged Chiral Ligands and Catalysts*; Ed. Q.-L. Zhou; Wiley- VCH: Weinheim, Germany, **2011**.

[4] For reviews, see: a) G. Helmchen, A. Pfaltz, *Acc. Chem. Res.* **2000**, *33*, 336-345. b) C. C. Bausch, A. Pfaltz, in *Privileged Chiral Ligands and Catalysts*; Ed.: Q.-L. Zhou; Wiley: Weinheim, Germany, **2011**, pp 221-256.

[5] J. Padevet, M. G. Schrems, R. Scheil, A. Pfaltz, *Beilstein J. Organ. Chem*. **2016**, *12*, 1185-1195 and references there in.

[6] For recent reviews, see: a) M. Diéguez, O. Pàmies, C. Claver, *Chem. Rev.* **2004**, *104*, 3189-3216. b) M. Diéguez, O. Pàmies, Acc. *Chem. Res.* **2010**, *43*, 312-322; c) P. W. N. M. van Leeuwen, P. C. J. Kamer, C. Claver, O. Pámies, M. Diéguez, *Chem. Rev.* **2011**, *111*, 2077-2118; d) M. Magre, O. Pàmies, M. Diéguez, *Chem. Rec*. **2016**, *16*, 1578-1590; e) O. Pàmies, M. Diéguez, *Chem. Rec*. **2016**, *16*, 2460-2481; f) J. Margalef, O. Pàmies, M. Diéguez, *Tetrahedron* **2016**, *72*, 2623-2631.

[7] a) O. Pàmies, M. Diéguez, C. Claver, *J. Am. Chem. Soc*. **2005**, *712*, 3646–3647; b) R. Bellini, M. Magre, M. Biosca, P.-O. Norrby, O. Pàmies, M. Diéguez, C. Moberg, *ACS Catal*. **2016**, *6*, 1701–1712.

[8] M. Magre, M. Biosca, O. Pàmies, M. Diéguez, *ChemCatChem*, **2015**, *7*, 114–120.

[9] a) D.-S. Wang, Q.-A. Chen, S.-M. Lu, Y.-G. Zhou, *Chem. Rev.* **2012**, *112*, 2557-2590; b) W. S. Knowles, R. Noyori, *Acc. Chem. Res.* **2007**, *40*, 1238-1239.

[10] a) D. Q. Pharm, A. Nogid, *Clin. Ther.* **2008**, *30*, 813-824 (Rotigotine); b) J. I. Osende, D. Shimbo, V. Fuster, M. Dubar, J. J. Badimon, J. Thromb. *Haemostasis* **2004**, *2*, 492-497 (Terutroban); c) S. B. Ross, S.-O. Thorberg, E. Jerning, N. Mohell, C. Stenfors, C. Wallsten, I. G. Milchert, G. A. Ojteg, *CNS Drug Rev*. **1999**, *5*, 213-232 (Robalzotan); d) B. Astier, L. Lambás Señas, F. Soulière, P. Schmitt, N. Urbain, N. Rentero, L. Bert, L. Denoroy, B. Renaud, M. Lesourd, C. Muñoz, G. Chouvet, *Eur. J. Pharmacol.* **2003**, *459*, 17-26 (Alnespirone).

[11] a) J. L. Renaud, P. Dupau, A.-E. Hay, M. Guingouain, P. H. Dixneouf, C. Bruneau, *Adv. Synth. Catal.* **2003**, *345*, 230-238; b) R. Hoen, M. van den Berg, H. Bernsmann, A. J. Minnaard, J. G. de Vries, B. L. Feringa, *Org. Lett.* **2004**, *6*, 1433-1436; c) X.-B. Jiang, L. Lefort, P. E. Goudriaan, A. H. M. de Vries, P. W. N. M. van Leeuwen, J. N. H. Reek, *Angew. Chem. Int. Ed.* **2006**, *45*, 1223-1227; *Angew. Chem.* **2006**, *118*, 1245-1249; d) A. J. Sandee, A. M. van der Burg, J. N. H. Reek, *Chem. Commun.* **2007**, 864-866; e) M. Revés, C. Ferrer, T. León, S. Doran, P. Etayo, A. Vidal-Ferran, A. Riera, X. Verdaguer, *Angew. Chem. Int. Ed.* **2010**, *49*, 9452-9455; *Angew. Chem.* **2010**, *122*, 9642-9645; f) Z. Wu, T. Ayad, V. Ratovelomanana-Vidal, *Org. Lett.* **2011**, *13*, 3782-3785; g) L. Pignataro, M. Boghi, M. Civera, S. Carboni, U. Piarulli, C. Gennari, *Chem. Eur. J.* **2012**, *18*, 1383-1400; h) D. J. Frank, A. Franzke, A. Pfaltz, *Chem. Eur. J.* **2013**, *19*, 2405-2415; i) M. J. Bravo, R. M. Ceder, G. Muller, M. Rocamora, *Organometallics* **2013**, *32*, 2632-2462; j) I. Arribas, M. Rubio, P. Kleman, A. Pizzano, *J. Org. Chem.* **2013**, *78*, 3997-4005; k) G. Liu, X. Liu, Z. Cai, G. Jiao, G. Xu, W. Tang, *Angew. Chem. Int. Ed.* **2013**, *52*, 4235-4238; *Angew. Chem.* **2013**, *125*, 4329-4332.

[12] a) E. Salom, S. Orgué, A. Riera, X. Verdaguer, *Angew. Chem. Int. Ed.* **2016**, *55*, 7988-7992; *Angew. Chem.* **2016**, *128*, 8120-8124; b) M. Magre, O. Pàmies, M. Diéguez, *ACS Catal.* **2016**, *6*, 5186-5190.

[13] J. Margalef, O. Pàmies, M. Diéguez, *Chem. Eur. J.* **2017**, *23*, 813-822.

[14] For reviews, see: a) X. Cui, K. Burgess, *Chem. Rev.* **2005**, *105*, 3272-3296; b) K. Källström, I. Munslow, P. G. Andersson, *Chem. Eur. J.* **2006**, *12*, 3194-3200; c) S. J. Roseblade, A. Pfaltz, *Acc. Chem. Res.* **2007**, *40*, 1402-1411; d) T. L. Church, P. G. Andersson, *Coord. Chem. Rev.* **2008**, *252*, 513-531; e) O. Pàmies, P. G. Andersson, M. Diéguez, *Chem. Eur. J.* **2010**, *16*, 14232-14240; f) D. H. Woodmansee, A. Pfaltz, *Chem. Commun.* **2011**, *47*, 7912-7916; g) Y. Zhu, K. Burgess, *Acc. Chem. Res.* **2012**, *45*, 1623-1636; h) J. J. Verendel, O. Pàmies, M. Diéguez, P. G. Andersson, *Chem. Rev.* **2014**, *114*, 2130-2169; i) C. Margarita, P. G. Andersson, *J. Am. Chem. Soc.* **2017**, *139*, 1346-1356

[15] A. Lightfoot, P. Schnider, A. Pfaltz, *Angew. Chem. Int. Ed.* **1998**, *37*, 2897-2899.

[16] For representative examples, see: a) J. Blankenstein, A. Pfaltz, *Angew. Chem. Int. Ed.* **2001**, *40*, 4445-4477; *Angew. Chem.* **2001**, *113*, 4577-4579; b) D.-R. Hou, J. H. Reibenspies, T. J. Colacot, K. Burgess, *Chem. Eur. J.* **2001**, *7*, 5391-5400; c) F. Menges, A. Pfaltz, *Adv. Synth. Catal.* **2002**, *344*, 40-44; d) M. C. Perry, X. Cui, M. T. Powell, D.-R. Hou, J. H. Reibenspies, K. Burgess, *J. Am. Chem. Soc.* **2003**, *125*, 113-123; e) W. Tang, W. Wang, X. Zhang, *Angew. Chem. Int. Ed.* **2003**, *42*, 943-946; f) Bunlaksananusorn, T.; Polborn, K.; Knochel, P. *Angew. Chem. Int. Ed.* **2003**, *42*, 3941-3943; *Angew. Chem.* **2003**, *115*, 4071-4073; g) D. Liu, W. Tang, X. Zhang, *Org. Lett*. **2004**, *6*, 513-516; h) W. J. Drury III, N. Zimmermann, M. Keenan, M. Hayashi, S. Kaiser, R. Goddard, A. Pfaltz, *Angew. Chem. Int. Ed.* **2004**, *43*, 70-74; *Angew. Chem.* **2004**, *116*, 72-76; i) K. Källström, C. Hedberg, P. Brandt, A. Bayer, P. G. Andersson, *J. Am. Chem. Soc.* **2004**, *126*, 14308-14309; j) S. McIntyre, E. Hörmann, F. Menges, S. P. Smidt, A. Pfaltz, *Adv. Synth. Catal.* **2005**, *347*, 282-288; k) S. Bell, B. Wüstenberg, S. Kaiser, F. Menges, T. Netscher, A. Pfaltz, *Science* **2006**,

311, 642-644; l) S. Kaiser, S. P. Smidt, A. Pfaltz, *Angew. Chem. Int. Ed.* **2006**, *45*, 5194-5197; *Angew. Chem.* **2006**, *118*, 5318 –5321; m) C. Hedberg, K. Källström, P. Brandt, L. K. Hansen, P. G. Andersson, *J. Am. Chem. Soc.* **2006**, *128*, 2995-3001; n) M. Engman, J. S. Diesen, A. Paptchikhine, P. G. Andersson, *J. Am. Chem. Soc.* **2007**, *129*, 4536-4537; o) J. Zhao, K. Burgess, *J. Am. Chem. Soc.* **2009**, *131*, 13236-13237; p) P. Tolstoy, M. Engman, A. Paptchikhine, J. Bergquist, T. L. Church, A. W.-M. Leung, P. G. Andersson, *J. Am. Chem. Soc.* **2009**, *131*, 8855-8860; q) W.-J. Lu, Y.-W. Chen, X.-L. Hou, *Adv. Synth. Catal.* **2010**, *352*, 103-107; p) Y. Zhang, Z. Han, F. Li, K. Ding, A. Zhang, *Chem. Commun.* **2010**, *46*, 156-158; r) D. Rageot, D. H. Woodmansee, B. Pugin, A. Pfaltz *Angew. Chem. Int. Ed.* **2011**, *50*, 9598-9601; *Angew. Chem.* **2011**, *123*, 9772– 9775; s) T. Zhou, B. Peters, M. F. Maldonado, T. Govender, P. G. Andersson, *J. Am. Chem. Soc.* **2012**, *134*, 13592-13595; t) J. Shang, Z. Han, Y. Li, X. Wang, K. Ding, *Chem. Commun.* **2012**, *48*, 5172-5174; u) X. Wang, Z. Han, Z. Wang, K. Ding, *Angew. Chem. Int. Ed.* **2012**, *51*, 936-940; *Angew. Chem.* **2012**, *124*, 960-964; v) Y. Zhu, K. Burgess, *RSC Advances* **2012**, *2*, 4728-4735; w) A. Schumacher, M. Bernasconi, A. Pfaltz, *Angew. Chem. Int. Ed.* **2013**, *52*, 7422-7425; *Angew. Chem.* **2013**, *125*, 7570-7573; x) M. Bernasconi, M. A. Müller, A. Pfaltz, *Angew. Chem. Int. Ed.* **2014**, *53*, 5385-5388; *Angew. Chem.* **2014**, *126*, 5489-5492; y) X. Liu, Z. Han, Z. Wang, K. Ding *Angew. Chem. Int. Ed.* **2014**, *53*, 1978-1982; *Angew. Chem.* **2014**, *126*, 2009-2013; z) J. Xia, G. Yang, R. Zhuge, Y. Liu, W. Zhang, *Chem. Eur. J.* **2016**, *22*, 18354-18357.

[17] More recently, the successful use Ir-catalysts modified with non-N-donor heterodonor P,S and P,O ligands in this reaction has been described. See: a) D. Rageot, D. H. Woodmansee, B. Pugin, A. Pfaltz, *Angew. Chem. Int. Ed.* **2011**, *50*, 9598–9601; *Angew. Chem.* **2011**, *123*, 9772–9775; b) M. Coll, O. Pàmies, M. Diéguez, *Chem. Commun.* **2011**, *47*, 9215–9217; c) M. Coll, O. Pàmies, M. Diéguez, *Adv. Synth. Catal.* **2013**, *355*, 143–160; d) J. Margalef, X. Caldentey, E. A. Karlsson, M. Coll, J. Mazuela, O. Pàmies, M. Diéguez, M. A. Pericàs, *Chem. Eur. J.* **2014**, *20*, 12201–12214; e) C. Borràs, M. Biosca, O. Pàmies, M. Diéguez, *Organometallics*, **2015**, *34*, 5321–5334; f) M. Biosca, M. Coll, F. Lagarde, E. Brémond, L. Routaboul, E. Manoury, O. Pàmies, R. Poli, M. Diéguez, *Tetrahedron* **2016**, *72*, 2623-2631.

[18] S.-M. Lu, C. Bolm, *Angew. Chem. Int. Ed.* **2008**, *47*, 8920-8923, *Angew. Chem.* **2008**, *120*, 9052-9055.

[19] See for example: a) M. Diéguez, J. Mazuela, O. Pàmies, J. J. Verendel, P. G. Andersson, *J. Am. Chem. Soc.* **2008**, *130*, 7208-7209; b) M. Diéguez, O. Pàmies, J. J. Verendel, P. G. Andersson, *Chem. Commun.* **2008**, 3888-3890; c) J. Mazuela, J. J. Verendel, M. Coll, B. Schäffner, A. Börner, P. G. Andersson, O. Pàmies, M. Diéguez, *J. Am. Chem. Soc.* **2009**, *131*, 12344-12353; d) J. Mazuela, A. Paptchikhine, O. Pàmies, P. G. Andersson, M. Diéguez, *Chem. Eur. J.* **2010**, *16*, 4567-4576; e) J. Mazuela, P.-O. Norrby, P. G. Andersson, O. Pàmies, M. Diéguez, *J. Am. Chem. Soc.* **2011**, *133*, 13634-13645; f) J. Mazuela, O. Pàmies, M. Diéguez, *Adv. Synth. Catal.* **2013**, *355*, 2569-2583; g) J. Mazuela, O. Pàmies, M. Diéguez, *ChemCatChem* **2013**, *5*, 2410-2417.

[20] Ligands **L1a**,**d-g** and **L2**-**L4a** had been previously successfully used in the allylic substitution (see, ref [7]) and the Ir-hydroboration (see, reference [8]). Ligands **L1a**-**c**, **L3**-**L4b** have been tested in the Ir-hydrogenation of β-enamides (see, ref [12b]).

[21] Ligands **L5**-**L6b** have been tested in the Ir-hydrogenation of β-enamides (see, ref [12b]). The new ligands **L5**-**L6a**, **c**-**g** and **L7a**-**g** are variations of them that include a bulky ^{t}Bu group in the oxazoline and new biaryl phosphite groups with different substituents and configurations.

[22] a) M. Simón, S. Jansat, G. Muller, D. Panyella, M. Font-Bardía, X. Solans, *J. Chem. Soc., Dalton Trans.* **1997**, 3755–3764; b) M. Murai, K. Okamoto, K. Miki, K. Ohe, *Tetrahedron* **2015**, *71*, 4432–4437.

[23] B. Schäffner, F. Schäffner, S. P. Verevkin, A. Börner, *Chem. Rev.* **2010**, *110*, 4554-4581.

[24] a) Y. Donde, J. H. Nguyen, WO2015048553A1, **2015**; b) F. Pohlki, U. Lange, M. Ochse, B. Behi, C.W. Hutchins, US2012040948A1, **2012**; c) P. T. Lansbury, C. J. Justman, WO2009036275A1, **2009**; d) J. Pontillo, Y. Gao, W.S. Wade, D. Wu, W.K. Eccles, US2006276454A1, **2006**; e) R. Kolanos, U. Siripurapu, M. Pullagurla, M. Riaz, V. Setola, B. L. Roth, M. Dukata, R.A. Glennona, *Bioorg. Med. Chem. Lett.* **2005**, *15*, 1987; f) D. C. Horwell, W. Howson, W. P. Nolan, G. S. Ratcliffe, D. C. Rees, H. M. G. Willems, *Tetrahedron* **1995**, *51*, 203; g) E. L. Plummer, N. Tonawanda, US4362744A, **1982**.

[25] a) E. S. Rovner, A. Wein, *J. Eur. Urol.* **2002**, *41*, 6–14; b) J. Wefer, M. C. Truss, U. Jonas, *World J. Urol.* **2001**, *19*, 312–318; c) C. J. Hills, S. A. Winter, J. A. Balfour, *Drugs* **1998**, *55*, 813–820; d) M. Gordaliza, P. A. García, J. M. Miguel del Corral, M. A. Castro, M. A. Gómez-Zurita, *Toxicon* **2004**, *44*, 441–459.

[26] a) D. H. Woodmansee, M. A. Müller, L. Tröndlin, E. Hörmann, A. Pfaltz, *Chem. Eur. J.* **2012**, *18*, 13780-13786; b) J.-Q. Li, X. Quan, P. G. Andersson, *Chem. Eur. J.* **2012**, *18*, 10609-10616.

[27] a) W.-J. Lu, Y.-W. Chen, X.-L. Hou, *Angew. Chem., Int. Ed.* **2008**, *47*, 10133-10136; *Angew. Chem.* **2008**, *120*, 10287-10290; b) F. Maurer, V. Huch, A. Ullrich, U. Kazmaier, *J. Org. Chem.* **2012**, *77*, 5139-5143; c) J. J. Verendel, J.-Q. Li, X. Quan, B. Peters, T. Zhou, O. R. Gautun, T. Govender, P. G. Andersson, *Chem. Eur. J.* **2012**, *18*, 6507-6513; d) ref [16u]; e) ref [18].

[28] The hydrogenation of **S16**-**S21** yields products with opposite configuration than those achieved with the other *E*-trisubstituted olefins studied (i.e. **S1**-**S3**). This behavior has been observed previously and it is attributed to the strong polarization of the double bond, see ref 14h.

[29] For successful examples, see: a) T.-Y. Yue, W. A. Nugent, *J. Am. Chem. Soc.* **2002**, *124*, 13692-13693 (lactams); b) W.-J. Lu, X.-L. Hou, *Adv. Synth. Catal.*

2009, *351*, 1224-1228 (acyclic amides); c) Q. Li, P. Wan, Y. He, Y. Zhou, L. Li, B. Chen, K. Duan, R. Cao, Z. Ahou, L. Qiu, *Asian J. Org. Chem*. **2014**, *3*, 774-783 (lactones and lactams); d) ref [16y] (lactones and lactams); e) ref [26b] (lactones).

[30] a) P. Cheruku, J. Diesen, P. G. Andersson, *J. Am. Chem. Soc.* **2008**, *130*, 5595–5599; b) A. Ganič, A. Pfaltz, *Chem. Eur. J.* **2012**, *18*, 6724–6728; c) ref [17c].

[31] It has been suggested that this isomerization process can proceed either via the formation of Ir-π-allyl intermediates or via protonation of the double bond at the terminal position, which gives a stabilized carbocation. a) ref 16b; b) J. M. Brown, A. E. Derome, G. D. Hughes, P. K. Monaghan, *Aust. J. Chem.* **1992**, *45*, 143-153.

[32] For successful applications, see: a) A. Paptchikhine, P. Cheruku, M. Engman, P. G. Andersson, *Chem. Commun.* **2009**, 5996-5998; b) ref [30b]; c) ref [17d]; d) ref [19c].

[33] For successful applications, see: a) P. Cheruku, S. Gohil, P. G. Andersson, *Org. Lett.* **2007**, *9*, 1659-1661; b) ref [30a].

[34] For sucesffull examples, see: a) ref [16j]; b) ref [19c].

[35] See for instance: a) A. Abate, E. Brenna, C. Fuganti, G. G. Gatti, T. Givenzana, L. Malpezzi, S. Serra, *J. Org. Chem.* **2005**, *70*, 1281-1290; b) K. Drescher, A. Haupt, L. Unger, S. C. Rutner, W. Braje, R. Grandel, C. Henry, G. Backfisch, A. Beyerbach, W. Bisch, WO Patent 2006/040182 A1, **2006**.

[36] G. J. H. Buisman, P. C. J. Kamer, P. W. N. M. van Leeuwen, *Tetrahedron: Asymmetry* **1993**, *4*, 1625-1634.

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